Risk stratification in early breast cancer in premenopausal and postmenopausal women: integrating genomic assays with clinicopathological features

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Abstract

Purpose of review

There is growing consensus that genomic assays provide useful complementary information to clinicopathological features in oestrogen receptor (ER)-positive breast cancers. Here, ongoing research with multigene tests used for postmenopausal breast cancer and new emerging prognostic and predictive markers for pre- and postmenopausal women are summarised.

Recent findings

Results of the TAILORx trial have shown that women with an intermediate risk score do not benefit from adjuvant chemotherapy. Prosgina has been further investigated in a contemporary patient population in postmenopausal women and its use has been extended for premenopausal women. The EndoPredict was extensively used in decision-impact studies showing that its use can potentially reduce the need for adjuvant chemotherapy. Several new genomic assays have been developed, with some of them showing promising use for women with early ER-positive breast cancer.

Summary

New areas of research for prediction of recurrence and risk stratification involve the development of immune gene signatures that carry modest but significant prognostic value. The recent expansion of high-throughput technology platforms including circulating tumour DNA/RNA and microRNA offer new opportunities to improve prediction models, particularly in women with ER-negative disease and premenopausal women. Genomic assays have clearly improved prognostication of early ER-positive breast cancer but it is clear that standard clinicopathological parameters are still very important when identifying patient for adjuvant chemotherapy.

Key words: genomic assay, prognosis, prediction, adjuvant chemotherapy, clinicopathological parameters

Introduction

Breast cancer is a heterogeneous disease and prediction of risk of recurrence depends on several clinicopathological factors: tumour size, histologic grade, lymph node involvement, and expression of both the oestrogen (ER) and on HER2 protein overexpression or gene amplification (or both) [1]. Traditionally these factors are used to determine what adjuvant treatment is necessary for early stage breast cancer. In most cases, patients with ER-positive breast cancer are offered endocrine therapy, and patients with HER2-positive tumours are offered both chemotherapy and anti HER2 therapies. However, determining which ER-positive, HER2-negative patients should be offered chemotherapy is a more complex question. Furthermore, there are no clinically useful prognostic signatures for ER-negative breast cancer, and drug-specific treatment response predictors also remain elusive.

Several multigene prognostic tests have been developed over the past two decades to improve and guide clinical treatment decisions with regard to systemic chemotherapy. In particular, these tests have been developed to improve prognostication of early-stage breast cancer in addition to clinicopathological features within the first five years of diagnosis. Oncotype DX [2], MammaPrint [3] and Genomic Grade Index [4], which are first-generation tests, are more accurate to predict specifically recurrence within the first 5 years after diagnosis than in later years. This has become a limitation with the availability of effective extended adjuvant endocrine therapies. Newer test, such as Prosigna [5], EndoPredict [6], Breast Cancer Index [7], possess better prognostic value for late recurrences while also remaining highly predictive of early relapse. An important aspect of genomic assays is the distinction between utility of these tests for prognosis (recurrence) and for prediction (treatment response). Some argue that genomic assays need to show distinctive predictive utility to determine who needs chemotherapy, with data deriving from prospective, randomised trials. However, treatment effects need to be assessed in terms of absolute benefits and thus a genomic test that is highly prognostic for recurrence (accurate stratification into low or high risk groups) is still highly predictive of the absolute benefit of treatment.

Therefore, the accurate stratification of patients into low and high risk groups is an important clinical questions since that determines, along with clinicopathological features, who should receive adjuvant chemotherapy. Another important aspect to consider is the presence of an intermediate risk group with some of the genomic assays. This risk group includes patients with an elevated risk of recurrence but at a level of clinical uncertainty because of lack of clear evidence of chemotherapy benefit. This review discuss several new findings with respect to risk stratification using genomic assays, in particular for postmenopausal women.

Clinicopathological features

Prognosis using clinicopathological features is clinically still important and should not be forgotten. It has been shown that genomic assays that incorporate clinical features perform substantially better in terms of prognosis than purely molecular assays. One of the most important clinical factor is lymph node involvement, followed by tumour size and grade [8, 9]. Despite many advances in the development of genomic assays, clinical factors continue to remain of importance when determining prognosis in early breast cancer.

More than 50% of recurrence in women with ER-positive disease occur 5 years after initial diagnosis. The use of clinicopathological features has been used to determine who is at risk of developing a late distant recurrence. An overview analysis of over 60000 women with ER-positive disease who received 5 years of endocrine therapy and remained disease free at 5 years reported the subsequent risk of distant recurrence [10]. Even in patients with small tumours and node negative disease, the estimated risk of distant recurrence between years 5 and 20 was 10% for those with low, 13% for those with intermediate, and 17% for those with high grades, respectively. The data were presented as risk categories mainly using tumour size categories (e.g. T1, T2), limiting precise estimates of risk for individual patients. Furthermore, the analysis included mainly a tamoxifen-treated population, which did not allow assessment of possible differences between tamoxifen and aromatase inhibitors (AIs) with regard to long-term risk.

More recently, we reported on the use of clinicopathological features for the prediction of late distant recurrences in a combined dataset of two large clinical trials, which compared an aromatase inhibitor with tamoxifen [11]. We developed a simple prognostic tool that stratifies patient into low, intermediate, and high risk of developing a late distant recurrence, with distinctively different 5-10 year risk for the three risk categories. The CTS5 tool is intended for clinicians to determine the risk of late distant recurrence and may help in the decision-making process about extended endocrine therapy (www.cts5-calculator.com).

Although the above studies have shown that the use of clinicopathological features are important, not just for prediction of late distant recurrences, it is widely accepted that these factors alone are inadequate for optimum patient management, especially as the management of breast cancer patients moves towards the era of personalised treatment. In the last two decades several genomic assays have been developed to improve prognostication of early breast cancer and several of them are recommended for clinical use by several expert panels.

Genomic assays

Oncotype Dx

The Oncotype Dx Recurrence Score has been developed for women with ER-positive, node-negative breast cancer and has been widely validated in several studies [2, 12-15]. This assay utilises expression measurements from 21 cancer-related genes to compute a recurrence score from 0 to 100, which can be categorized into low risk (<18), intermediate risk (18 to 30),

or high risk (≥31) groups. Several studies, including a meta-analysis of four prospective studies, have shown that the use of the Oncotype Recurrence Score leads to treatment changes in chemotherapy use, in particular in ER-positive, HER2-negative, and lymph node negative disease [16-18].

In a comprehensive head-to-head comparison of several prognostic genomic assays [19], The Oncotype Dx Recurrence score was only significantly prognostic in women with ER-positive, lymph node negative disease for the first 5 years after diagnosis. For those with lymph-node positive disease or for the prediction of late distant recurrences, the Oncotype Dx Recurrence Score did not provide any substantial prognostic value when compared to Prosigna or EndoPredict. The prognostic value of the Oncotype Dx Recurrence Score has extensively been investigated [12, 20] and more recently the predictive value of the assay has been reported.

The TAILORx study randomised women with ER-positive, HER2-negative, lymph-node negative disease and intermediate recurrence scores (11-25) to endocrine therapy alone or to endocrine therapy plus chemotherapy [21]. The results showed that women in this intermediate risk group by Oncotype did not benefit from additional chemotherapy compared to those that only received endocrine therapy, with very similar 9-year invasive disease-free survival. Looking at different sub-group analyses, the authors did not find any significant interaction between treatment and several prognostic clinical features, except for age, making it unclear whether younger women might still benefit from chemotherapy in the intermediate risk group. This finding is supported by data from the SOFT [22] and TEXT [23] trials wherein premenopausal women at intermediate or high risk have substantial improvement in outcome with ovarian function suppression after chemotherapy. Of note, the ranges used to define the risk groups in the TAILORx study are different from those traditionally used (see above), and hence increasing the size of the intermediate risk group substantially. However, using traditional clinical parameters, most of these women would not have been regarded as having an intermediate risk of developing a recurrence and hence would not have been candidates for chemotherapy in the first place.

To further evaluate the clinical utility of Oncotype Dx Recurrence Score for node-positive patients, the RxPONDER trial (SWOG S1007) enrolled ER-positive, HER2-negative patients with 1–3 involved regional lymph nodes and low-to-intermediate recurrence scores (≤25). Patients are being randomly allocated to endocrine therapy alone or to endocrine therapy plus chemotherapy. The results from this study are still outstanding. Results from a large prospectively designed registry study showed that women with ER-positive, HER2-negative, 1-3 lymph node positive disease with a Recurrence score between 18-30 and who were treated with chemotherapy had a significantly lower recurrence rate compared to untreated patients [24].

Prosigna

The Prosigna assay has been developed for postmenopausal women with ER-positive, lymph node-negative or node positive disease who were treated with tamoxifen [5]. Several validation studies have shown the prognostic utility of this assay for the prediction of early (years 0-5) [25] and late distant recurrences [26] and significantly distinct risk stratification for women with lymph-node negative and positive disease [19]. The Prosigna assay has

recently been further validated in a Danish cohort of postmenopausal women with lymph-node negative and positive disease who have received 5 years of endocrine therapy [27]. In this population based cohort, the Prosigna assay identified 37% of patients with a one positive lymph node and 15% of patients with two positive nodes as low risk, with very favourable outcomes when treated with adjuvant endocrine therapy alone. This analysis did not include any women with a low risk of recurrence (node-negative, tumours smaller than 20mm, and grade 1 tumours) and the risk stratification observed here are different than those in validation studies from large clinical trials [25, 28]. The observational Oslo1 study furthermore confirmed that in particular the intrinsic Prosigna sub-types improve classification of patients with ER-positive, HER2-negative, and lymph node negative breast cancer into distinct risk groups [29]. The Prosigna provided substantial prognostic value for distant recurrence in a comparative analysis, classifying patients into distinct low, intermediate and high risk groups with significantly different 10-year outcomes [19].

The Prosigna assay was also investigated in premenopausal women of whom the majority had lymph-node positive disease and who received cyclophosphamide-based adjuvant chemotherapy [30]. The results showed that continuous Prosigna ROR score was prognostic in high-risk premenopausal women with breast cancer but no interaction with treatment was observed in the overall study population. However, in a subset analysis, for women with ER-positive, Her2-negative disease a significant benefit of chemotherapy was observed for those who had a high ROR score (high risk group > 40). Furthermore, a strongly significant interaction was observed between Prosigna intrinsic subtypes and chemotherapy use. Women with a basal-like or luminal B sub-type had a distinct benefit from cyclophosphamide-based chemotherapy.

The predictive ability of the Prosigna assay is currently being investigated in the OPTIMA trial [31]. Initial analysis of the preliminary OPTIMA trial [32] showed that the Prosigna assay was ranked highest in terms of research value and is therefore being investigated further in the full trial.

EndoPredict

The EndoPredict assay was developed in women with ER-positive, lymph node-negative or positive, and HER2-negative disease [6, 33]. It has been validated in postmenopausal women who received endocrine therapy for the prediction of early and late distant recurrences [34-38] and in premenopausal women who received endocrine therapy plus chemotherapy [39]. It is one of the few genomic assays that has only two risk categories, with generally classifying more women into the high risk group, specifically in node-positive disease. However, the two risk groups should not be regarded as a disadvantage of the test, rather the opposite. There have been several observational and decision impact studies over the past year investigating the EndoPredict assay. In a small study of 120 patients, the impact of the EndoPredict on chemotherapy recommendations was investigated [40]. 35% of women classified as being high risk by the Nottingham Prognostic Index, and therefore candidates for chemotherapy, were classified into the low risk group by EndoPredict, indicating that the use of EndoPredict can reduce the need for adjuvant chemotherapy in women with ER-positive, HER2-negative

disease. Other decision impact studies have shown similar results where the use of the EndoPredict assay in the clinic reduced chemotherapy recommendations by 30-40% [41, 42].

Other assays

Other genomic assays, such as the Breast Cancer Index [7, 43], MammaPrint [3], Genomic Grade Index [4], have also been investigated for ER-positive breast cancer. Newer genomic assays that have reported the results over the past year include the OncoMasTR [44], the Curebest 95GC Breast assay [45], and a 95-gene assay [46]. The OncoMasTR incorporates three genes with clinical parameters (tumour size and nodal status) into the final assay. Initial validation has shown that OncoMasTR provides significant prognostic information for (late) distant recurrence and provides differential risk stratification (low versus high risk), in particular for node negative disease and to a lesser extent in those with lymph node positive disease [44]. The Curebest is a pure molecular assay and was validated for the prognostic performance for the prediction of early recurrence only (<5 years), with significant differential classification in to low and high risk groups [47]. An interesting study developing a novel 95 gene assay using pathology samples from the TEAM trial has recently reported their results [46]. The final 95 gene test incorporates information on nodal status and stratifies patients into low and high risk groups, with significantly different 10-year distant recurrence risk. Although the assay needs to be further validated in an independent patient cohort, an exciting aspect of this assay is that they have identified several genes and pathways suitable for targeted therapies, indicating that the test might predict response to drug-specific chemotherapy [46].

Conclusion

In summary, all validation studies for the Oncotype Dx Recurrence Score, Prosigna, and EndoPredict examined prognosis in prospective clinical trials in which at least one arm received a standard endocrine treatment and although the tumour blocks were tested retrospectively, the trials themselves were prospective in design and constitute level IB evidence for prognostic validity [48]. For patients with ER-positive disease who receive endocrine therapy alone, all three assays identify a low risk population with a favourable outcome at 5 or 10 years after diagnosis. A low risk assay test result is therefore actionable, and the decision to withhold chemotherapy is supported by this evidence. The same is true for categorisation into high risk groups by these tests, in particular by Prosigna and EndoPredict, where the addition of chemotherapy is warranted. Any information obtained from any of the genomic assays must still be interpreted in the context of clinicopathological features of the tumour. Several guidelines, including the American Society of Clinical Oncology working group [49], emphasise that the prognostic utility of these tests are to be interpreted with clinicopathological features. Although the Oncotype Dx Recurrence score has been most widely investigated and validated assay for ER-positive, HER2-negative, lymph node negative disease, newer second generation assays such as Prosigna and EndoPredict have significant advantages over Oncotype in terms of prognostic value for lymph-node positive disease, and in particular for the prediction of late distant recurrence. To determine

who is going to develop a late distant recurrence is an important clinical question and although none of the genomic assays was particularly trained to predict late recurrence, some of them have shown to accurately stratify patients into respective risk categories. Clinical parameters that are available to all clinicians have been shown to be of great importance for the prediction of late recurrences. Most guidelines now endorse genomic assays [49-52] in particular for lymph-node negative disease. When a decision is made about a genomic assay, it is important to use only one as risk group stratification between two tests are different when more than one test is used [53]. The identification of clinically useful markers for women with triple negative breast cancer is still one of the more important unsolved questions. Better progress has been made for premenopausal women although a specifically developed genomic assay for younger breast cancer patients still does not exist. However, several new technologies, including miRNA, circulating tumour DNA, RNA sequencing, may improve and extended the current prediction models.

Key bullet points

- Genomic assays help for the improvement of prognostication of ER-positive breast cancer.
- Clinical parameters are still very important to determine prognosis and genomic assays should be used in conjunction with these features.
- Chemotherapy effects need to be assessed in terms of absolute benefits and a genomic test that is highly prognostic for recurrence is therefore highly predictive of the absolute benefit of treatment.
- Several studies have shown that chemotherapy benefit can be investigated in a non-randomised fashion.
- Several new technologies may improve and extended the current prediction models specifically for women with ER-negative disease.

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Conflicts of interest

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